REMARKS

Claims 1-3 are pending in the instant application. Claims 1-3 have been rejected. Claims 1-3 have been canceled. Claims 11-12 have been added. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §103

Claims 1-3 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Coligan et al. (Current Protocols in Immunology, Green Publishing Associates and Wiley-Interscience, New York, 1991; pages 2.1.1-2.1.3, 2.1.9-2.1.11, and 2.1.17-2.1.22) in view of U.S. Patent 5,077,216; Zwaldo et al. (1987) (IDS Reference BA); Zwaldo et al. (1992) (IDS Reference AX); Hogger et al. ((1998) *Pharma. Res.* 15:296-302); and Droste et al. ((1999) *Biochem. Biophys. Res. Commun.* 256:110-113) as evidenced by Sulahian et al. ((Sept. 2000) *Cytokine* 12:1312-1321). It is suggested that Coligan et al. teach an antibody-sandwich ELISA to detect soluble antigens, and ELISAs are useful for screening biological fluids (*e.g.*, plasma) for antigen content. The Examiner acknowledges that Coligan et al. do not teach a method for detecting an early signaling event in an inflammatory response, comprising detecting CD163 with antibodies directed against CD163, wherein said antibody is monoclonal antibodies MAC2-158 or MAC2-48 and wherein the CD163 is soluble. It is suggested that the '216 patent teaches a method for detecting a p155 human mononuclear phagocyte-specific antigen using the monoclonal antibodies MAC2-158 and MAC2-48, wherein the monocytes were from human plasma. It is further suggested that Zwaldo et

al. (1987) teach that the RM3/1 antigen is useful for monitoring an early signaling event in an inflammatory response in a patient and Zwaldo et al. (1992) teach monitoring the appearance of RM3/1-positive macrophages in blood between 24 and 72 hours post-inflammatory response. The Examiner suggests that Hogger et al. teach that injection of glucocorticoids into primates or human volunteers results in an increase of RM3/1-positive blood monocytes within 6 hours and therefore it would have been obvious to one of skill in the art that Hogger et al. teach that expression of RM3/1 antigen is indicative of an early signaling event in the inflammatory response. It is further suggested that Droste et al. teach that CD163 is expressed on human monocytes and macrophages, wherein upon an inflammatory stimulus, this protein is shed rapidly from the cell membrane and exists as a soluble protein. The Examiner suggests that it would have been obvious, based upon the combined teachings of these references to arrive at the claimed invention. Applicants respectfully disagree with this rejection.

Collectively, the '216 patent, Zwaldo et al. (1987), Zwaldo et al. (1992), Hogger et al. and Sulahian et al. teach expression patterns for CD163 on the cell surface of monocytes and macrophages. However, none of these references teach or suggest that cell surface expression of CD163 correlates in any way with CD163 levels shed *in vivo* in a patient exposed to an inflammatory stimulus. Moreover, while Droste et al. teach shedding of CD163 *in vitro* (see page 112, first paragraph under "Discussion") and provide that "[s]hedding of CD163 by phorbol esters might serve as an *in vitro* model for an additional insight into the function of CD163 in monocyte cells" (see page 113, column 1, lines 12-

14), this reference does not teach that CD163 is shed *in vivo* in a patient exposed to an inflammatory stimulus.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cited references simply fail to provide a basis for establishing a *prima facie* case of obviousness.

First and foremost, the combined teachings of the cited references do not teach or suggest that CD163 is shed *in vivo* upon exposure to an inflammatory stimulus and found as a soluble protein in plasma. This is contrary to the requirement that all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). MPEP §2143.03.

Furthermore, prior to the present Disclosure, there would have been no reasonable basis for expecting that soluble CD163, or any other member of the scavenger receptor cysteine-rich (SRCR) family, was shed *in vivo* into the plasma, because as

Droste et al. specifically point out, "[t]he present study demonstrates for the first time the shedding of a member of the SRCR family." See page 112, first column, first line of second paragraph. Moreover, the prior art, as evidenced by the teachings of Kubo et al. ((1999) *Am. J. Res. Crit. Care Med.* 159:267-274; enclosed herewith), indicates that *in vitro* shedding experiments are not wholly indicative of *in vivo* solubilization of proteins. In particular, Kubo et al. demonstrate that L-selectin is shed less easily *in vivo* than *in vitro*, concluding that the protease that cleaves L-selectin may be partially inhibited by antiproteases in the blood (see page 273, second column, last paragraph). Therefore, the *in vivo* context and presence of protease inhibitors are variables that prevent the direct extrapolation of the *in vitro* analysis of Droste et al. to conclude that CD163 is shed *in vivo* in a patient exposed to an inflammatory stimulus.

Thus, the Examiner's conclusion that it would have been obvious, based on the prior art teachings, to detect soluble CD163 in a biological sample, in particular plasma, is no more than an unsubstantiated theoretical possibility, which is insufficient to support this rejection. *Cf. Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1344, 68 USPQ2d 1154, 1159 (Fed. Cir. 2003) ("a theoretical possibility or 'metaphysical doubt', ... is insufficient to create a genuine issue of material fact.")

Therefore, in an earnest effort to highlight Applicants' inventive finding that soluble CD163 is in fact shed *in vivo* and a detectable elevation in the level of *in vivo* shed, soluble CD163 in response to the inflammatory stimulus is indicative of an early signaling event in the inflammatory response cascade in

a patient, Applicants have canceled claims 1-3 and added new claims 11 and 12. New claims 11 and 12 are supported by previously pending claims 1-3 and the Disclosure at pages 9-11 of the specification.

Because the cited prior art references fail to teach or suggest soluble CD163is shed *in vivo*, these references fail to teach or suggest all the claim limitations (see MPEP 2143). Thus, the cited reference cannot be held to make the present invention obviousness under 35 U.S.C. 103(a). It is therefore respectfully requested that this rejection be withdrawn.

II. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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